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Evaluation of Crohn's disease activity

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Chapter 10

Summary

This thesis describes the diagnostic value of MRI in the evaluation of the inflammatory activity of Crohn's Disease (CD). Like Nuclear Medicine, MRI may detect specific features of intestinal CD lesions that are crucial in the therapy decision making process, particularly in the choice of the new biological "target" therapies. Quantification of the activity of CD lesions, their characterization (oedema versus fibrosis) and assessment of their intestinal extent and complications, are widely considered the major issues in the management of the disease. We have demonstrated with different studies that all these issues can be fully addressed by optimizing at the outmost MRI techniques for evaluation of the bowel.

Similarly, by using specific radio-labeled tracers, NM has shown the potential to assess the presence of specific inflammatory cytokines in CD lesions "in vivo", in order to address clinicians towards a rationale choice of the most effective biological therapy. The possible association of the two imaging modalities, now achievable with the new PET-MRI units, could lead to a more comprehensive in vivo characterization of the disease, with still unexplored potentials.

Chapter 1. This is an introduction on the main pathologic and clinical aspects of CD. Recent hypotheses on the pathogenesis of the disease are shortly described, as well as the main microscopic and macroscopic CD features and phenotypes, according to the Vienna Classification. The pharmacological treatment and the newest biological agents (monoclonal antibodies) are here mentioned. The complexity of the diagnostic work up of the disease, related to its longitudinal extent in the small and large bowel and to the typical transmural extent of inflammation with frequent complications, are discussed. MRI intrinsic advantages related to the availability of multiple imaging parameters (T1, T2 weighted, etc) highly sensitive for tissue inflammation are outlined. Similarly, the specific diagnostic capabilities of NM in CD are explained, mostly related to the use of different radiopharmaceuticals that allow assessment and visualisation of the intestinal inflammatory process in vivo.

Chapter 2. In this paper we proposed the first clinical-radiological study on CD activity, based on the analysis of several MRI parameters. In 20 adult patients affected by CD and studied with MRI, five different T1 and T2-weighted MRI parameters were analyzed and tested at the level of the inflamed bowel wall for the assessment of disease activity, including wall thickening, degree of wall Gd-enhancement, T2 wall signal intensity, T2 signal of mesenteric fat. Each one of these MR parameters turned out to be statistically correlated with the

“biological” activity, expressed as positivity of two or more acute phase reactants ($p < 0.001$, r values between 0.78 to 0.96).

At that time (2000), only two previous early preliminary papers had been published on this subject. In the ten following years, more than 120 clinical-radiological papers have been published on MRI-CD activity. To date, MRI seems to be the most complete and powerful radiological tool to detect inflammatory changes in human tissues, and specifically in CD.

In **Chapter 3** it is described a large and complex study comparing the efficacy of different MRI parameters (both T1-weighted and T2-weighted) in the overall assessment of CD. Fifty-nine patients affected by Crohn disease were examined with MRI after oral administration of a superparamagnetic contrast agent. MRI evaluation of CD included either the detection of lesions site and length and complications in the small and large bowel (morphologic evaluation), as well as the assessment of the severity of lesions inflammation (evaluation of disease activity). T2-weighted MR was 95% accurate, 98% sensitive, and 78% specific for detection of ileal lesions. Agreement between T1- and T2-weighted images ranged from 0.77 for ileal lesions to 1.00 for colic lesions. T2-weighted signal intensities of the wall and mesentery correlated with biologic activity ($P < .001$, r 0.774 and 0.712, respectively), as well as Gd-enhancement ($P < .001$, r 0.751). Results were extremely satisfactory for both T1 and T2-weighted parameters, suggesting that MRI had the capability of evaluating the site, extent and activity of the disease with different parameters like no other radiological imaging modality. Disease activity was detected by MRI somehow similarly to NM. Differently from NM, however, MRI had the added value of offering an excellent morphological display of the lesions and their complications, in the small and large bowel.

In **Chapter 4** it is described and suggested the use of a specific MRI technique for the evaluation of the bowel, called “double contrast MR Enterography”, effective in the evaluation of IBD, and particularly of CD. The rationale of this technique is the contemporary optimization of both T1 and T2-weighted imaging parameters. Most of the published papers on MRI, in fact, underestimate T2-weighted parameters being predominantly focused on the amount of wall Gd-enhancement. Wall enhancement assessable on T1-weighted images, it is certainly crucial in the detection of the inflamed wall, but it is not the only pathologic event. Detection of wall oedema or fibrosis, better assessable on T2-weighted rather than T1-weighted images, is equally relevant for the therapy decision process of CD. Therefore, the optimization of T2-weighted imaging is of paramount importance in the evaluation and characterization of CD. Currently, the detection of wall fibrosis is considered a contraindication to several biological treatments and in most of the cases a major indication

for surgical resection. On the other hand, the presence of wall oedema may predict a positive response to medical treatments.

In **Chapter 5** we have briefly reviewed the pathophysiology and the new therapeutic approaches to IBD. The importance of tumour necrosis factor- α (TNF α), a highly proinflammatory molecule, in the pathogenesis of inflammation is reviewed. Genetic factor, particularly the association between NOD2 gene mutations on chromosome 16 and increased susceptibility to CD were also outlined. The management of patients with IBD and the potential therapeutic efficacy of the monoclonal antibody anti-TNF α (infliximab) was discussed. From the new therapeutic achievements the diagnostic flow charts were critically discussed and updated. The final diagnostic assessment of IBD proposed in this paper was still based on conventional guidelines, although a very early introduction of MRI was suggested for the diagnosis of CD in doubtful cases. Interestingly very recently (2013) the newest clinical-radiological guidelines (ECCO-ESGAR joint committee) have confirmed the primary role of MRI in the diagnosis of most of the aspects of CD and mainly for the assessment of CD activity.

Chapter 6. The monitoring of the therapeutic response is another major issue in the clinical management of the disease. In active phases of the disease, an increased production and release of TNF α by macrophages and monocytes of the lamina propria has been described. In order to visualise the presence of TNF α within the gut mucosa in patients with active CD candidate for immunotherapy with a chimeric human/mouse monoclonal antibody anti-TNF α (Infliximab, Remicade®), was labelled with ^{99m}Tc-technetium obtaining a stable product. Seven patients with active CD and candidate for immunotherapy with Infliximab were studied. Images of the abdomen were acquired at 6 to 20 hrs after i.v. injection of about 10 mCi of ^{99m}Tc-Infliximab and a week later, all patients were also studied with ^{99m}Tc-HMPAO-labelled autologous white blood cells (WBC). Despite the disease activity documented by endoscopy and elevated CDAI values, a significant ileal ^{99m}Tc-Infliximab accumulation was observed only in 5 patients, whereas a significant uptake of radiolabelled WBC was detected in 8 out of 10 patients. Therefore the degree of ^{99m}Tc-Infliximab uptake by the inflamed bowel evaluated at 20 hrs post injection was less than that seen with labelled WBC and with a different distribution. Likely, more studies are necessary to clarify the mechanism of action of anti-TNF α monoclonal antibodies.

Chapter 7. In this paper on cell trafficking in CD, the present and future capabilities of MRI and NM in the evaluation of the inflammatory process of CD and the potential value of their integration are discussed and reviewed.

Different scintigraphic methods of imaging cells involved in the pathogenesis are described. The radiopharmaceuticals can be divided into non-specific radiopharmaceuticals for inflammation and specific radiopharmaceuticals that directly image lymphocytes involved in the process. General, "nonspecific" radiopharmaceutical for inflammation include radiolabeled white blood cells, IgG-imaging, monoclonal antibody-imaging, ^{18}F -FDG,, while "specific" radiopharmaceuticals are targeted for a certain cytokine or chemokines involved in the patho-physiology of CD, such as IL2-imaging, TNF α -imaging, imaging E-selectin, etc. Finally, an update on other imaging modalities, and particularly MRI, in the evaluation of Crohn's disease activity, is provided. Although MRI cannot directly detect inflammatory cells, it has shown a high sensitivity in detecting the macroscopic signs of inflammation at the level of the intestinal wall affected by Crohn's disease and Ulcerative colitis. The current diagnostic value of MRI in the detection of inflamed bowel segment and in the assessment of CD activity, as well the potentials MR spectroscopy, MR diffusion imaging and MR molecular imaging, are briefly discussed. MRI has great potentials in characterization of the Crohn's disease, being able to assess microscopic structural wall changes, such as oedema and fibrosis, ipervascularity, capillary permeability, diffusion of water molecules, and likely, in the next years, specific molecular abnormalities.

Chapter 8. In this study on pediatric CD for the first time MRI was used for a direct comparative study between pediatric and adult patients, by evaluating either morphological and activity findings of the intestinal disease. The safety of MRI makes it useful to monitor disease in pediatric population, as well as to monitor effects of biological therapies. Forty-three adult and 43 pediatric patients were studied with the same MRI technique and extensively evaluated with clinical and endoscopic examinations as well. All the small and large bowel intestinal segments were analyzed. The site of the lesions and their activity, as shown by MRI, were directly compared. Results were surprising, interesting and original. Involvement of terminal ileum was observed in 100% adult patients (43/43) versus 58% (23/43) of pediatric ones ($P < 0.0001$). Conversely, the colon was diseased in 84% of pediatric patients versus 64% of adults, In particular, left colonic segments were significantly more involved were the descending colon (53% versus 21%, $P < 0.01$) and the rectum (67% versus 23%, $P < 0.0001$). In children the maximal disease activity was found in left colonic segments while in adults in the terminal ileum. Thus MRI showed a more extensive and severe involvement of the left colon in children, but of the distal ileum in adults. These relevant differences emerged between the two populations suggesting a possible phenotypic and genetic difference.

Finally, in **Chapter 9**, we have discussed the potential usefulness of the newest imaging parameters able to assess intestinal motility, molecular structure and angiogenesis at the level of the inflamed bowel loops. By using Diffusion Weighted Imaging (DWI), MRI can detect differences in the motility of water molecules at the level of the diseased bowel wall. Moreover, MR molecular imaging and MR spectroscopy, although still experimental, are very promising for the evaluation of IBD, due to possibility to analyze and characterize the molecular structure of the inflamed intestinal wall. Differentiation between intestinal oedema and fibrosis or between ulcerative colitis and Crohn's disease colitis could hopefully be easier by using these new imaging parameters. Both PET–MRI and MR molecular imaging, nowadays purely experimental and mostly focused on oncologic imaging, could lead to a deeper knowledge of the inflammatory process of CD.

Chapter 11

Conclusions

To date, MRI seems to be the most complete and powerful imaging tool to detect inflammatory changes in human tissues and specifically in CD. The high sensitivity of MRI for inflammatory tissues is related to the availability of different imaging parameters, mainly fluid-sensitive (T2-weighted) and gadolinium-enhanced ones, which are able to view the intestinal wall inflammation, fibrosis and edema in different ways. Thanks to these parameters, MRI can detect intestinal oedema and hypervascularity, like no other imaging modalities. The value and diagnostic utility of the T1 and T2-weighted imaging in the evaluation of inflammatory disease and characterization of the intestinal bowel wall have been specifically and extensively analyzed in various chapters of the thesis (chapter 2, 3 and 4). Several T1 and T2-weighted parameters, either morphological or functional, have been tested for the evaluation of disease activity, including wall thickening, degree of wall Gd-enhancement, T2 signal intensity of the intestinal wall and mesenteric fat. In our experience these MRI parameters turned out to be significantly correlated with the “biological” activity of CD, which is widely considered a reliable index of disease activity.

Tissue inflammation may be then easily assessed with different MRI parameters, to detect oedema, vascularization or fibrosis at the level of the pathological wall. In addition, new imaging parameters and sequences are continuously introduced in MRI. For example, using Diffusion Weighted Imaging (DWI), MRI can detect differences in the motility of water molecules at the level of the bowel wall affected by CD. Moreover, MR molecular imaging and MR spectroscopy, although still in an experimental phase, seem very promising for the evaluation of IBD, due to possibility to analyze and characterize the molecular structure of the inflamed intestinal wall (chapter 9). Only updated and advanced MRI systems, however, are currently able to offer the widest range of imaging parameters for assessing inflammation, able not only to differentiate the intestinal wall edema by fibrosis, but also to quantify the degree of parietal vascularization and angiogenesis, to detect subtle differences in the motility of the water molecules with DWI and molecular abnormalities with MR spectroscopy.

Definitely, the potentials of MRI in the detection of CD inflammation are vast and destined to expand in the next years, but they will be appreciated and fully understood only in the light of the most recent advances in clinical research. A close synergy and osmosis between

clinical and radiological knowledge will certainly be the key to many future advances in the clinical-diagnostics research. For too many years the clinical management of any disease, and more specifically of CD, has lead to a disjunction between the clinical research and the morphological-radiological research. Nuclear Medicine instead, historically has been more widely linked to the clinical research, likely due to a more direct biological approach. PET–MRI, nowadays purely experimental and mostly focused on oncologic imaging, could lead to a deeper knowledge of the inflammatory process of CD. Specific radiopharmaceuticals targeted for a certain cytokines or chemokines involved in the patho-physiology of CD, such as IL2-imaging, TNFa-imaging, etc, will likely be more and more used in the clinical and experimental diagnostic evaluation of CD, In the coming years advanced NM, functional MRI or molecular imaging will likely be able to guide clinicians in the choice of the most effective and specific biological therapy.

In the coming years, it is expected that radiologists, while maintaining their technical knowledge, will cooperate more closely with gastroenterologists and, on the other hand, gastroenterologists will be increasingly involved in issues of imaging. Probably, the boundaries between clinical and radiological sciences will become less and less defined, as is already the case in nuclear medicine. At the same time, integration of different imaging modalities, such as MRI and NM, will surely open further horizons in the evaluation and understanding of the inflammatory process of Crohn's disease.

A deeper integration between NM, MRI and clinical research will surely provide new information and knowledge on this and other diseases. The junction between morphological and molecular imaging is very close by.